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Critically Appraised Topic

Are biologics more effective than corticosteroids for intra-articular treatment of osteoarthritis?

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Summary

Intra-articular corticosteroids are an effective treatment for equine osteoarthritis, however, there is increasing evidence for the effectiveness of other treatments such as biologics. Whilst current evidence does support biologics and their use in patients diagnosed with osteoarthritis, there remains to be a lack of evidence regarding their long-term outcomes and the efficacy of their use as a treatment, especially when compared to corticosteroids. This paper reviewed the evidence comparing intra-articular corticosteroids and biologics in the treatment of equine osteoarthritis and found that whilst they are both effective treatments, more evidence directly comparing them is required.

Refining the question

Do biologics, such as autologous conditioned serum and autologous processed plasma, show an improved clinical outcome (defined as a reduction in lameness and/or fewer co-morbidities) and prognosis compared to corticosteroids when treating osteoarthritis in equids?

Strategy for searching the evidence

For both corticosteroids and biologics, three databases were searched on 18/11/2019; CAB Direct, Scopus and PubMed. Full search strategies can be seen in **Table 1** with inclusion and exclusion criteria found in **Table 2**.

TABLE 1: Three databases were systematically searched for terms relating to equine, biologics and corticosteroids

Journal	Biologics search	Corticosteroids search
CAB Direct	(horse or equine or equid) AND (osteoarthritis or OA) AND (intra-articular or IA) AND (IRAP or interkeukin-1 receptor antagonist)	(horse or equine or equid) AND (osteoarthritis or OA) and (intra-articular or IA) and (corticosteroid or steroid or dexamethasone or prednisolone or methylprednisolone or triamcinolone or betamethasone)
Scopus	(horse or equine or equid) AND (osteoarthritis or OA) and (intra-articular or IA and IRAP or interleukin-1 receptor antagonist)	(horse or equine or equid) AND (osteoarthritis or OA) and (intra-articular or IA) and (corticosteroid or steroid or dexamethasone or prednisolone or methylprednisolone or triamcinolone or betamethasone)
Pubmed	((((horse OR equine OR equid)) AND (osteoarthritis OR OA)) AND (intra-articular OR OA)) AND (IRAP OR interleukin-1 receptor antagonist)	((((horse OR equine OR equid)) AND (osteoarthritis OR OA)) AND (intra-articular or IA)) AND (corticosteroid OR steroid OR dexamethasone OR prednisolone OR methylprednisolone OR triamcinolone OR betamethasone)

Quality and quantity of evidence found

From searching the aforementioned databases and applying the inclusion and exclusion criteria (**Table 2**), four articles on biologics and five papers on corticosteroids were used in this critical appraisal. All articles on biologics were prospective randomised controlled trials (**Table 3**). For corticosteroids, four articles were prospective studies (two of which were randomised) and one a retrospective nonrandomised study.

TABLE 2: Exclusion and inclusion criteria which were applied to studies on interleukin-1 receptor antagonist protein biologics and corticosteroids

Biologics	
Inclusion	Relevant to the question, multi-animal study, *in vivo* study, papers from 2004 onwards, uses biologics for treatment of OA.
Exclusion	Treatment other than IRAP or other biologics, papers that are not relevant to the question, papers that are not in English, single case studies, in vitro studies and duplicates.
Corticosteroids	
Inclusion	Relevant to the question, multi-animal study, *in vivo* study, papers from 1997 onwards, uses corticosteroids for treatment of OA.
Exclusion	Treatment other than corticosteroids, papers that are not relevant to the question, in vitro studies, papers not in English, single case reports and duplicates.

TABLE 3: Following the exclusion/inclusion criteria being applied to the search results, four articles studying interleukin-1 receptor antagonist protein biologics were included in this critical appraisal

Biologics		
Author	Study	Findings
Frisbie *et al*. (2007)	Prospective blinded randomised controlled trial Experimentally induced OA	Investigated the treatment of experimentally induced osteoarthritis (OA) in horses with either autologous conditioned serum (ACS) or placebo (Phosphate Buffered Saline; PBS) as control. 16 horses were split into two groups of 8; placebo (PBS) or treatment (ACS). The two treatment groups were divided further with 4 having OA induced into one middle carpal joint with the other a sham operated treatment. All had intra-articular injections at 14, 21, 28- and 35-day intervals. Those in the ACS treatment group received ACS into the OA induced joint and placebo into the other sham-operated joint. Those in the control group all received PBS. Looking at clinical, biochemical and histological parameters there was a significant improvement in the degree of lameness detected on day 70 vs the OA affected placebo-treated joints.
Bertone *et al*. (2014)	Prospective double-blinded randomised controlled trial Naturally occurring OA	Investigated the treatment of osteoarthritis in 40 client-owned horses with either a placebo of 0.9% saline solution or autologous conditioned protein solution (APS). Treatment groups were broken down into two groups; APS treatment group (n = 20) and saline control group (n = 20). Results showed that lameness grades were significantly improved in the joints of the APS treatment group compared to the control group who showed no significant change.
Lasarzik *et al*. (2018)	Prospective randomised controlled trial Naturally occurring OA	Evaluating the effectiveness of two ACS protocols of which frequency of intra-articular ACS injection is being explored. 12 horses were split into two groups: • Group 1: 1 intra-articular injection of ACS given every week for 3 weeks. • Group 2: 3 intra-articular injections of ACS were given at 2-day intervals It was found that whilst 2-day interval dosing appeared to be slightly advantageous over a weekly dosing regimen due to the increases in IL-1ra and a decrease in IL-1β, further studies should be carried out.

These articles consisted of one cohort study and four clinical trials, of which one was blinded (**Table 4**).

Overall, the quality of these papers was good (Murad *et al*. 2016).

Can this evidence be applied to my case population and conclusions?

Currently, there are no studies that directly compare the effectiveness of biologics and corticosteroids when treating equine osteoarthritis (OA). Corticosteroids are commonly used as a therapy for osteoarthritis in horses and, in general, can be very effective. Their efficacy is dependent on the corticosteroid used, the dose administered, the type of joint, the duration of treatment and the degree of pathology within the joint. Corticosteroids act at the level of phospholipase A2 to block the production of inflammatory mediators produced from the cyclooxygenase and lipoxygenase pathways as well as having many other anti-inflammatory effects (Clegg and Booth 2000). In general, it seems like corticosteroids combined with hyaluronan or PSGAGs are usually effective in early stages of OA (Richardson and Dyson 2011). In comparison, biologics such as autologous conditioned serum are seen to work at a more specific part of the inflammatory pathway to increase anti-inflammatory cytokine concentrations (Hraha *et al*. 2011). An example would be the interleukin-1 (IL-1) receptor antagonist. IL-1 is a cytokine involved in the pro-inflammatory pathway, and so by minimising its effect as well as providing anti-inflammatory mediators, it promotes a homeostatic environment within the joint.

During the last decade, treatments for osteoarthritis using biologics have become increasingly more popular with their use growing in frequency, and with favourable anecdotal results (Richardson and Dyson 2011). In one study out of 428 practitioners, 36.2% use biologics when patients were nonresponsive to corticosteroids (Ferris *et al*. 2011). However, Ferris *et al*. draw on practitioners' choice of treatment for equine OA and so it is important to consider factors that will affect those choices, such as efficacy, marketing and client desires.

Whilst this critically appraised topic (CAT) was originally comparing the efficacy of corticosteroids vs. biologics, the issue of treatment timing became evident. One hypothesis is that biologic treatments are typically started later in the disease process where other treatment options have failed. Therefore, the OA will have progressed to a point where other treatment options may also struggle to provide an improved clinical outcome. Without further studies implicating the use of biologics as a treatment when clinical signs first present, it is difficult to ascertain their effectiveness as a first-line treatment, and so further studies relating to the stage of OA that biologics are used for treatment are required. Another factor limiting the use of biologics is their increased cost (Nelson and Goodrich 2014) in comparison with corticosteroids; in one study, Orthokine® (an autologous conditioned serum) was mainly used in the treatment of joint pain when cost was of no issue to clients (Ferris *et al*. 2011). Without substantial evidence proving its efficacy in early OA, it is understandable that it is not used preferentially over corticosteroids.

It should be noted that some of the studies presented here were investigating experimentally induced OA. However, similar improved clinical outcomes were found whether the animal being treated had naturally occurring or induced OA.

TABLE 4: Following the exclusion/inclusion criteria being applied to the search results, five articles studying corticosteroids were included in this critical appraisal

Corticosteroids		
Author	Study	Findings
Frisbie *et al*. (1997)	Prospective controlled clinical trial Experimentally induced OA	18 horses aged 2–7 years were used in this study; each had an osteochondral chip fragment induced into a randomly assigned intercarpal joint, they were then randomly assigned to one of three treatment groups. Group 1: placebo control. Bilateral treatment of intra-articular polyionic fluid was performed into the intercarpal joint. Group 2: Triamcinolone Acetonide (TA) control group. Intra-articular polyionic was injected into joints where a chip fragment had been created. TA fluid was also injected in the contralateral intercarpal joint. Group 3: TA treatment group where intra-articular TA was injected into the chip fragmented joint and the contralateral intercarpal joint was injected with polyionic fluid. Compared with horses in the control and TA control groups, horses in the TA treatment group were significantly less lame. Both intra-articular and remote site administration had favourable effects on synovial fluid, synovial membrane and articular cartilage morphological parameters (compared to placebo treatment).
Todhunter *et al*. (1998)	Prospective controlled clinical trial Experimentally induced synovitis	In this study, synovitis was induced in 10 ponies with lipopolysaccharide (LPS). Methylprednisolone acetate (MPA) alone was injected into select joints, and LPS with MPA injections administered at the final administration to the treatment group to investigate presence of pathological changes against an LPS control group. There was no significant difference between groups on histopathology. However, both LPS and LPS/MPA treatments groups had moderate to severe inflammatory changes compared to the MPA treated and control group which had mild to no inflammatory changes. In the MPA treatment group there was increased protein and collagen synthesis and decreased proteoglycan synthesis.
Labens *et al*. (2007)	Retrospective nonrandomised cohort study Naturally occurring OA	Investigated intra-articular treatment with corticosteroids alone or intra-articular corticosteroids with hyaluronate (HA) into distal tarsal joints in 51 horses, hospitalised with lameness due to osteoarthritis. The greatest improvement was observed in those that had mild to moderate signs of osteoarthritis in the tarsometatarsal and centrodistal joints, as well as those that had received less frequent IA injection into the centrodistal joint.
Grauw *et al*. (2015)	Prospective randomised blinded controlled clinical trial Naturally occurring OA	This study investigated 80 client owned horses with a clinical history of osteoarthritis. Two treatment groups were examined for clinical soundness; one group was treated with intra-articular TA alone and the other treated with intra-articular TA and HA. Those treated with TA and HA achieved a success rate of 64.1% compared to TA treatment with a success rate of 87.8% with success being defined as a reduction in lameness and effusion scores.

One study investigated the effects of corticosteroids on the treatment of induced synovitis (Todhunter *et al*. 1998). This study was included as whilst it is not a direct model of OA, synovitis has been implicated in the structural degradation of the joint during OA pathogenesis (Wenham and Conaghan 2010) and the progression of OA (McIlwraith *et al*. 2012). Due to this, the investigation of corticosteroids on synovitis is relevant to this CAT.

In conclusion, corticosteroids can be an effective first-line treatment, with biologics being used when corticosteroids fail or when funds are less restricted. However, due to the lack of literature directly comparing biologics and corticosteroids in the treatment of OA, further studies should be carried out earlier on in the disease process to compare the two treatments. Studies could focus on directly comparing the efficacy of biologics and corticosteroids when administered in early OA, deleterious or positive effects on joint pathophysiology, return to clinical soundness, and long-term efficacy.

Author's declaration of interests

No conflicts of interest have been declared.

Ethical animal research

Not applicable to this critically appraised topic.

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None.

Authorship

R. Lewis contributed to study design, data analysis and interpretation, and preparation of the manuscript. G.F. White contributed to study design, executed the study, data analysis and interpretation, and preparation of the final manuscript. C. B. Gómez Álvarez contributed to data interpretation

and preparation of the manuscript. All authors approved the final version.

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